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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,036	09/30/2002	Paul R. Sanberg	LAY-014PCTUS	5509

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EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,036	SANBERG ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 7-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Applicant's response and amendment to claims filed on June 28, 2006 have been acknowledged. Claims 1-4 and 7-17 were previously pending. Applicant has amended claims 1-3, 7, 10, 12, 14, 15, and 17 and has added new claims 18 and 19. Following the amendment, claims **1-4** and **7-19** are pending and under examination in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Oath/Declaration

The newly submitted declaration filed on June 28, 2006 has been entered. The deficiencies of record have been rectified.

Withdrawn Claim Objections and Rejections

The objection to claim 15 as set forth at p. 3 of the previous office action is hereby withdrawn in view of Applicant's amendment to the claim.

The declaration filed on June 28, 2006 under 37 CFR 1.131 is sufficient to overcome the Simm (102(a)) reference. Accordingly, the rejection of claims 1, 3, 4, 7-12, 14-15 and 17 under 35 U.S.C. 102(a), as set forth at pp. 3-5 of the 12/29/2005 office action, is hereby withdrawn.

Maintained Claim Rejections

Claim Rejections - 35 USC § 102

The rejection of claim 17 under 35 U.S.C. 102(b) as being anticipated by CA 2213780 (the '780 publication), as set forth at p. 5 of the 12/29/2005 office action, is maintained for reasons of record. Further, new claim 18 is also included in this rejection for reasons of record.

In the response filed 06/28/2006, Applicants argue that the '780 publication does not disclose the broader differentiable neuronal cell types, besides dopaminergic neurons presented in the publication, that are necessary for the treatment of stroke and neurodegenerative disorders. Further, applicants assert that there appears to be "an admission of non-enablement for human cells" by the '780 publication. Therefore, Applicants argue that the '780 publication is not enabling for the broad treatment of all human neurodegenerative disease nor for the use of human neural stem cells for transplantation into humans because "[a]ll the experimental work was conducted only in rats and mice." Applicants assert in the 1.131 declaration that "many pharmaceutical and other treatments in stroke animal models have not translated into successful

therapeutics in humans. *Nevertheless, this stroke model is the only widely accepted model.*" [emphasis added]

Applicants' argument has been fully considered but it is not found persuasive.

In response to applicants' argument that the reference purportedly fails to demonstrate enablement regarding certain features of applicant's invention, it is noted that the features upon which applicants rely (i.e., treatment of humans/implantation of cells into humans; use of human neural stem cells only; treatment of neurodegenerative diseases *other than* Parkinson's disease) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). For example, the fact that mainly dopaminergic neurons were identified in the "olfballs", or GABAergic neurons or even TH-positive neurons, is irrelevant because the claims merely recite "neuronal cells" (as in claim 17), or more specifically "neural stem cells" (claim 18). Dopaminergic neurons derived from neural precursor cells would thus meet the limitations recited in the claims. Thus, the fact that the publication only "proposes" other cells types is irrelevant, as is the fact that the method of identifying the GABAergic was not fully explained. Identification of different neuronal and non-neuronal cell types using antibodies specific for distinguishing cell characteristics – such as the presence of tyrosine hydroxylase (TH) for identifying sympathetic/dopaminergic neurons, etc. – is well known and practiced in the art. Additionally, the claims, as written, are directed to a method of replacing nerves lost to "neurodegenerative disease, trauma, ischemia, *or* poisoning" (emphasis added),

and therefore the treatment of Parkinson's disease, which is a neurodegenerative disease, would again meet the recited limitation of the claims. In fact, the rodent model of Parkinson's disease disclosed in the '780 publication, wherein dopaminergic neurons are destroyed by infusing 6-hydroxydopamine into the striatum, is a widely-accepted model for the disease. So, in effect, the publication also teaches a method of replacing nerves lost to "poisoning" as well as "neurodegenerative disease." Further, the claims recite a "method of replacing in an *individual's* nervous system", wherein the broadest interpretation of "individual" includes non-human animals. Therefore, the so-called "admission of non-enablement for human cells" is irrelevant because the method is disclosed as fully successful in rats, which are individuals.

Further, in response to applicants' argument regarding the enablement of the '780 publication, the MPEP (§ 2121.01) states that "[a] reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention."" *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). Further, the MPEP (§ 2164.02) states that "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention.... the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating..." See *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436,

1441 (Fed. Cir. 1995). By Applicants' own admission, certain animal models are widely accepted and used for studying particular diseases and disorders as well as for predicting the outcome of treatment for a particular disease or disease state when applied to humans. The animal models employed by the '780 publication are similarly well-established and widely accepted animal models for studying Parkinson's disease and treatment thereof. As such, one of ordinary skill in the art could have determined that the '780 publication's disclosure was predictive of treatment of neurodegenerative disease and thus could make and use the claimed invention. Accordingly, the rejection of instant claims 17 and 18 is maintained.

Claim Rejections - 35 USC § 103

The rejection of claims 1-4 under 35 U.S.C. 103(a) as being obvious over US Patent 5,851,832 ('832 patent) in view of Sanberg et al. (1997) and in further view of Grabowski et al. (1994), as set forth at pp. 6-9 of the 12/29/2006 office action, is maintained for reasons of record.

In the response filed 06/28/2006, Applicants argue that the '832 patent provides no example of successful transplantation of neural cells into humans, "just rodent models which do not have a reasonable expectation of success in providing therapeutic benefit in humans." Similarly, Applicants argue that the Sanberg et al. teachings are based on the implantation of hNT cells in an animal model, and therefore also do not provide a reasonable expectation of success in humans. Applicants additionally question the applicability of both the rat model and the source of cells employed by

Grabowski et al. to human therapy, and add that there was no experimental group in which transplantation occurred at least 3 months following injury. Finally, Applicants argue that there is no suggestion to combine the teachings to produce all of the elements in the claims, particularly in regard to teachings needed to support the reasonable expectation of success in humans.

Applicants' argument has been fully considered but it is not found persuasive. Firstly, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted, as above, that the features upon which applicant relies (i.e., treatment of humans) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). For example, the broadest reasonable interpretation of the claims as written, which recite treatment of a "patient", would include the treatment of non-human animals such as rodents. Additionally, the Examiner fails to see how the fetal rat neocortical cells used by Grabowski et al. are of "questionable applicability for the cell types mentioned in claim 3" because the transplanted fetal rat telencephalic (neural) cells taught by Grabowski *are* "fetal non-human mammalian cells", *as recited* in amended claim 3. If Applicants argue that such cells are not applicable to human therapy, then Applicants thus appear to be suggesting the non-enablement of their own method claim.

Secondly, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be

established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the '832 patent clearly discloses treatment neurodegenerative disease and brain injuries, such as stroke, in humans. The Sanberg et al. reference clearly suggests that a greater overall number of transplanted cells is desirable and will produce a better outcome. Similarly, the teachings of Grabowski et al. suggest that a longer delay following ischemic injury prior to the transplantation surgery is also desirable, as the damaged brain area is more hospitable to the transplanted cells. Based on these teachings and those of the '832 patent, all of which used widely-accepted animal models for stroke, the skilled artisan would have a reasonable expectation of success for the treatment of stroke in humans.

Furthermore, assuming *arguendo* that the references were not predictive of treatment in humans, the MPEP (§ 2121.01) explicitly states that: "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." Beckman Instruments v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). Therefore, "a non-enabling reference may qualify as prior art for the purpose of determining obviousness under 35 U.S.C. 103." Symbol Techs. Inc. v. Opticon Inc., 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991). Additionally, at the time the instant invention was made, the ability to harvest, enrich, and clonally expand

multipotent neural stem cells in tissue culture was known and practiced in the field, and experts in the field of neurology and neurosurgery repeatedly suggested the use of such stem cells for the treatment of central nervous system repair based on successful transplantation studies in animal models of stroke and neurodegenerative disease, as extensively discussed in the "Background" section of the '832 patent and also in Snyder and Macklis, which was referenced in the 12/29/2006 office action (*Clin Neurosci*, 1996; 3: 310-316). As such, Applicants argument that the "hypothetical" examples described in the '832 patent do not provide a reasonable expectation of success is not persuasive, because the person of ordinary skill in the art *at the time the invention was made* would have predicted success in humans based upon the presumably enabled methods claimed in the US '832 patent and upon successes in relevant animal models described in the patent therein. Accordingly, the rejection of claims 1-4 is maintained.

The rejection of claims 7-17 under 35 U.S.C. 103(a) as being obvious over Sanberg and Borlongan (1996) in view of US Patent 5,851,832 ('832 patent) and in further view of Uchida et al. (1995), as set forth at pp. 9-14 of the 12/29/2006 office action, is maintained for reasons of record. Additionally, new claims 18 and 19 are included in this rejection for reasons of record.

In the response filed 06/28/2006, Applicants argue that the teachings of Sanberg and Borlongan and those of the '832 patent are limited to rodent models, which do not have a reasonable expectation of success in human treatment. As such, Applicant appears to be arguing the enablement of the cited references. Applicants also note that

the Uchida et al. reference is limited to teachings of using syngenic neural plate tissue for transplantation in transgenic mice, and therefore again argue that the mouse model would not convey a reasonable expectation of success in humans. Finally, Applicants argue that there is no suggestion in the references to modify the references and arrive at the claimed invention.

Applicants' argument has been fully considered but it is not found persuasive. The response to Applicants' argument that the teachings based on animal models do not provide a reasonable expectation of success for treatment in humans has been addressed above. Again, the MPEP (§ 2121.01) explicitly states that: "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." Beckman Instruments v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). Therefore, "a non-enabling reference may qualify as prior art for the purpose of determining obviousness under 35 U.S.C. 103." Symbol Techs. Inc. v. Opticon Inc., 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of Sanberg and Borlongan clearly state that significant improvement in sensimotor and

cognitive functioning was achieved in rats transplanted with human hNT cells, similar to what is observed when fetal striatal cells are used for the treatment of neurodegenerative disease such as Huntington's, thus indicating that treatment in humans is not only possible but also successful. Additionally, by Applicants' own admission in the 1.131 declaration that, despite some shortcomings, the animal model employed by these references is the only art-accepted animal model of stroke, and therefore is the best predictor of success for human treatment. As for the Uchida reference, the Examiner is uncertain why the Applicants question the applicability of the transplanted cell tissues as they pertain to "the cells mentioned in claim 3", because this claim is not addressed in this rejection. However, such cells are recited in new claims 18 and 19. The mesencephalic neural plate tissue used by Uchida comprises both "neural stem cells" and "neural crest cells" and *is* "fetal non-human mammalian cells," and thus would meet the limitation of "a combination thereof" recited in these claims. Moreover, the fact that Uchida et al. implanted cells of the same genetic makeup as the recipient is irrelevant because: a) there is no recited limitation for non-syngenic (i.e., not genetically similar) cells recited in the claims, and b) this reference was not relied upon for teaching which type of cell to implant, those teachings are found in the '832 patent and in the Sanberg and Borlongan reference. The Uchida reference is provided merely to provide evidence that transplanted cells have the capacity to migrate to sites distant from the site of implantation, be it by intraventricular or parenchymal delivery. See, for example, p. 4 of the 12/29/2006 office action, referencing Synder and Macklis (*Clin Neurosci*, 1996; 3: 310-316), stating that "donor-derived stem cells transplanted into

brains of mice subjected to hypoxic-ischemic damage preferentially migrate and integrate extensively within the large ischemic (i.e. damaged) areas that typically span the length of the injured hemisphere." Accordingly, this feature associated with the transplanted cells would be expected to occur upon simply administering the cells, as is written in claim 15. Thus, the person of ordinary skill in the art at the time the invention was made would have both motivation to combine the teachings of the cited references *and* a reasonable expectation of success for the treatment of humans to arrive at the claimed invention. As such, the rejection of claims 7-19 is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claim 15 has been amended and recites a treatment method for "a person who has experienced brain damage due to a hemorrhagic or *thrombotic* stroke". Applicant states in the response filed June 28, 2006 that support for the phrase "hemorrhagic or

thrombotic" can be found on page 1, lines 18-19. However, the Examiner cannot find literal support for "thrombotic" stroke at this page or any other of the instant application, nor in any of the priority documents. Therefore, the specification as originally filed does not have adequate written description for the claimed invention reciting brain damage due to thrombotic stroke.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
September 13, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER